REMARKS

Claims 1, 15, 20-24, 26-28, 30, 31, 45 and 60-70 are pending in this application. Claims 2-14, 25, 29, 40, 41 and 46-49 have been canceled. Claims 1, 15, 20, 21, 23, 26, 27, 30 and 45 have been amended. Claims 60-70 have been added. Support for the language "malignant brain tumors" in claims 15 and 62 can be found on page 6, paragraph [0024]. Support for the language "solid" in claims 60-70 can be found on page 2, paragraphs [0007], [0008] and [0009]. No new matter has been added. In view of the foregoing amendments and the following remarks, Applicants believe that the asserted rejections should be withdrawn and that all pending claims 1, 15, 20-24, 26-28, 30-31, 45 and 60-70 are in condition for allowance.

The disclosure is objected to as not complying with the requirements of 37 C.F.R. §§ 1.821 through 1.825 as indicated in the Notice to Applicant mailed on October 12, 2005. Applicants submit concurrently herewith a revised sequence listing in computer readable form (CRF) as well as a paper copy of the sequence listing.

35 U.S.C. § 112 Rejections

Claims 1-3, 6-7, 15, 20-27, 30-31, 40-41 and 45-59 stand rejected under 35 U.S.C. § 112, first paragraph, for purported lack of written description. The Examiner asserts that there is no support in the specification for the amendment of the claims from "administering therapeutically effective amounts *in unit form*" to "administering to the animal or human a therapeutically effective amount." Claim 1 has been amended to add back the recitation "in unit dosage form," thus overcoming this rejection.

Claims 6-7 and 30-31 stand rejected under 35 U.S.C. § 112, second paragraph, for purported indefiniteness. The Examiner asserts that claims 6 and 30 are rendered indefinite by the phrase "R refers to analogue substitutions" because the nature of R and R_2 are not defined. Claim 6 has been canceled. Claim 30 has been amended to delete the recitation "R refers to analogue substitutions," thus obviating this rejection. Because claim 31 depends from claim 30, it's rejection also has been obviated.

Claims 1-3, 6-7, 15, 20-27, 30-31, 40-41 and 45-59 stand rejected under 35 U.S.C. § 112, first paragraph, for purported lack of enablement. The Examiner alleges that,

although the specification is enabling with respect to specific secretase inhibitors, such as L-685,458, DAPT, DAPM, JLK-6, OM99-2, Z-VLL-CHO, GL189 and P10-P4'statV, it is not enabling for all secretase inhibitors. The Examiner asserts, at page 5, third full paragraph of the Office Action, that "given that one could not determine a general mechanism of anti-angiogenic action for all protease inhibitors, that gamma proteases themselves are highly enigmatic, and given the breadth of the working examples provided, it flows logically that one would be unduly burdened with experimentation to determine the effect of any and all protease inhibitors...".

Applicants respectfully point out that the claimed methods are not directed to the use of a broad class of protease inhibitors, but rather to methods of administration of secretase inhibitors, which make up a minuscule fraction of protease inhibitors. In this regard, the specification is clear that secretase inhibitors inhibit angiogenesis and provide examples of specific secretase inhibitors which inhibit angiogenesis. Hence, Applicants submit that it is irrelevant whether the mechanism of how beta- and gamma-secretase inhibitors inhibit angiogenesis is understood by those skilled in the art. Rather, what is relevant is Applicants' finding that secretase inhibitors inhibit angiogenesis, and thus one skilled in the art would not be unduly burdened with experimentation to practice the claimed invention. The specification provides methods of confirming the anti-angiogenic properties of secretase inhibitors, and methods of administering such compounds to treat solid tumors to thereby reduce the volume of tumors that are dependent on angiogenesis. Based on the detailed disclosure in the specification, and the discovery that secretase inhibitors are anti-angiogenic, one skilled in the art could readily practice the claimed methods. The below additional remarks should resolve any remaining concerns on the Examiner's part.

It is noted that claim 61 has been added which recites specific inhibitors.

35 U.S.C. 102/103 Rejections

Claims 1-3, 6-7, 25-27, 30-31, 40-41 and 59 stand rejected under 35 U.S.C. § 102(a) for purported anticipation by Jundt et al. Claims 1-3, 6-7, 15, 20-27, 30-31, 40-41 and 45-59 stand rejected under 35 U.S.C. § 103(a) for purported obviousness over Jundt et al. At page 7, third full paragraph, the Examiner, states that "Jundt et al. do not expressly teach an

in vivo method of treating a tumor in an animal or human in need thereof and using a carrier in addition to the secretase inhibitor." Claims 1-3, 6-7, 15, 20-27, 30-31, 40-41 and 45-59 stand rejected under 35 U.S.C. § 103(a) for purported obviousness over Weng et al. Applicants respectfully traverse these rejections to the extent that they are applied to the amended claims.

The claims as amended are directed to methods of treating a solid tumor in an animal or human by administering a carrier and at least one secretase inhibitor in order to inhibit angiogenesis concomitant with solid tumor growth. In contrast, Jundt et al. is silent with respect to any connection whatsoever between the administration of γ-secretase inhibitors and inhibition of angiogenesis to reduce the volume of solid tumors in an animal or human. Nowhere does Jundt et al. teach or suggest administration of a carrier and a γ-secretase inhibitor generally, or a carrier and DAPT specifically, in order to inhibit angiogenesis in an animal or human in need thereof to reduce the volume of solid tumors. Rather, Jundt et al. solely discloses that the γ-secretase inhibitor DAPT blocks activation of Notch signaling to control tumor growth in hematopoietic malignancies, such as Hodgkin and anaplastic large cell lymphoma, which are not solid tumors.

As stated in the Jundt et al. abstract, as well as being generally understood by those skilled in the art at the time of filing of the instant application, Notch receptors are key regulators of hematopoietic differentiation and development, whereby Notch activation induces either stem cell renewal or differentiation towards lymphoid lineages. Additionally, truncated Notch alleles have been implicated in the development of human T-cell leukemia, as well as Hodgkin and certain lymphomas, all of which are non-solid malignancies.

As understood by those skilled in the art, a cancerous solid tumor is an adherent mass of malignant cells that when a critical mass of the adherent malignant cells is reached, angiogenesis is stimulated. In contrast, a hematopoietic malignancy is a dispersed malignancy of individual malignant cells in which individual malignant cells spread within a particular compartment, first in the vasculature compartment and then in the lymphatic compartment. Therefore, hematopoietic malignancies are not localized at a stationary site for angiogenesis to have any effect. Thus, it is recognized by those skilled in the art that only solid tumors stimulate angiogenesis and, indeed, require angiogenesis in order for the solid

tumor to grow beyond a few millimeters. It is further recognized that solid tumors cannot grow beyond the size of a pinhead (1 to 2 cubic millimeters) without the induction of angiogenesis. Additionally, there is a direct correlation between the density of tumor vessels and an adverse prognosis in patients afflicted with solid tumors, such as breast, colon, lung, kidney, bladder and head and neck tumors. One skilled in the art, therefore, understands that angiogenesis is not stimulated or required for the proliferation of hematopoeitic malignancies, such as T-cell leukemias, Hodgkin and lymphomas.

Similar to the Jundt et al. abstract, nowhere does Weng et al. teach or suggest a method of treating a solid tumor by inhibiting angiogenesis comprising administering to an animal or human a therapeutically effective amount of a secretase inhibitor effective to inhibit angiogenesis and to reduce the volume of the solid tumor. Rather, Weng et al. solely teaches that presenilin inhibitors, such as DAPT, suppress the growth of an N-terminally deleted form of NOTCH1, using cell lines derived from Notch1-associated T-cell lymphoblastic neoplasms (T-ALLs), a hematopoietic, non-solid malignancy. Here again, Weng et al. is silent with respect to administering a carrier and a beta- or gamma-secretase inhibitor generally, or a carrier and DAPT in particular, to inhibit angiogenesis in an animal or human in order to reduce the volume of solid tumors.

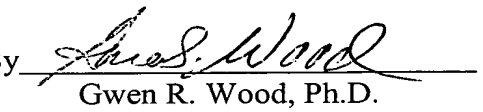
Thus, from the teaching of Notch signal inhibition in Jundt et al. and Weng et al., and the disclosure therein of completely different malignancies, there is no disclosure or suggestion of angiogenesis inhibition using secretase inhibitors, as disclosed in the present application and as recited in the presently amended claims. In view of Jundt et al. alone or in combination with Weng et al., there would be no motivation for one of ordinary skill in the art to administer a secretase inhibitor to inhibit angiogenesis and to thereby treat solid tumors including malignant tumors of the brain, breast, colon, kidney, bladder, head or neck. Jundt et al. and Weng et al. only disclose treating hematopoietic malignancies, not solid tumors, of which inhibition of angiogenesis would not apply.

Applicants therefore submit that neither Jundt et al. nor Weng et al., either alone or in combination, teaches or suggests the claimed methods directed to treating a solid tumor in an animal or human by administering a carrier and at least one secretase inhibitor in order to inhibit angiogenesis concomitant with solid tumor growth.

In view of the foregoing amendments and remarks, it is respectfully submitted that all pending claims 1, 15, 20-24, 26-28, 30-31, 45 and 60-70 in the present application comply with the requirements of Section 112 and are distinguishable from the cited prior art. Accordingly, reconsideration and withdrawal of the rejection and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

THE WEBB LAW FIRM

By 

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